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Risk of Connective Tissue Disorders among Breast Implant Patients

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In a US retrospective cohort study (1960–1996), 351 (4.8%) of 7,234 patients with breast implants and 62 (2.9%) of 2,138 patients who had undergone other types of plastic surgery reported subsequent rheumatoid arthritis (RA), scleroderma, systemic lupus erythematosus, or Sjögren's syndrome (relative risk = 2.0, 95% confidence interval (CI): 1.5, 2.8). Risks of RA, scleroderma, and Sjögren's syndrome were elevated both before and after 1992, when the Food and Drug Administration changed the status of breast implants to investigational. When records for these diseases were retrieved (35–40% retrieval rate) and blindly reviewed, two expert rheumatologists assessed only a minority of the cases as being "likely" (e.g., regarding RA, 16.5% for implant patients and 23.5% for comparison patients). Recalculation of incidence rates using "likely" diagnoses found relative risks of 2.5 (95% CI: 0.8, 7.8) for RA, scleroderma, and Sjögren's syndrome combined and 1.9 (95% CI: 0.6, 6.2) for RA only. When the proportions deemed "likely" were applied to all self-reports, the estimated relative risks were 2.0 (95% CI: 0.7, 5.4) for the three disorders combined and 1.3 (95% CI: 0.5, 3.8) for RA. These results indicate that self-reports of connective tissue disorders are influenced by reporting and surveillance biases. Given the diagnostic complexities of these diseases, excess risks, if they exist, may be beyond detection even in a study of this size.

arthritis, rheumatoid; breast implants; connective tissue diseases; risk; scleroderma, systemic; Sjögren's syndrome

Abbreviations: CI, confidence interval; CTD(s), connective tissue disorder(s); RR, relative risk.

Considerable controversy has surrounded the long-term safety of silicone breast implants. Concerns regarding cancer risk have centered around breast cancer, hematopoietic malignancies, and sarcomas (1–4). Clinical reports (5–15) have raised additional concerns regarding the long-term risks of connective tissue disorders (CTDs). Although a number of epidemiologic investigations have assessed these relations (16–35), they have been hindered by methodological limitations, including small sample sizes, limited follow-up, and imprecise information on either the exposures or the outcomes of interest.

In 1992, the US Congress directed the National Institutes of Health to undertake an investigation to assess the long-term safety of silicone breast implants. In response, the National Cancer Institute designed an epidemiologic follow-up investigation focused on the relation between cosmetic breast implants and subsequent cancer occurrence and overall mortality patterns. Several previous publications addressed these initial research goals (1, 2, 36). While it was not the primary focus of the study, systematic follow-up of a large group of women who had received breast implants provided investigators with an opportunity to assess CTDs, many of which have received attention as possible consequences of exposure to silicone implants. In this paper, we address the impact of timing and types of breast implants on

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the long-term risks of various CTDs, considering both patient reports and medical verification of these conditions.

MATERIALS AND METHODS

This retrospective cohort study has been described previously (2, 36). Institutional review boards at the National Cancer Institute and the organizations involved in data collection approved the study. Eligible study subjects comprised women who had had initial bilateral augmentation mammoplasty before 1989 at one of 18 plastic surgery practices in six areas (Atlanta, Georgia; Birmingham, Alabama; Charlotte, North Carolina; Miami and Orlando, Florida; and Washington, DC). Since breast cancer was a primary outcome of interest, patients who had received implants following treatment for breast cancer were not included. A total of 13,488 eligible study subjects were identified, comprising all augmentation mammoplasty patients at each practice who met the eligibility criteria. In addition, 3,936 comparison subjects from these same practices were identified, comprising similar-aged patients who had undergone other types of plastic surgery not involving silicone during the same time period. The major types of plastic surgery included abdominoplasty or liposuction, blepharoplasty or rhytidectomy (operations for removal of wrinkles on the face and neck), and rhinoplasty, otoplasty, mentoplasty, or genioplasty (operations involving the nose, ear, or chin). The number of comparison patients was considerably lower than the number of implant patients, since the emphasis of the study was on cancer outcomes, for which external comparison incidence rates are available.

Trained abstractors reviewed medical charts and entered data directly into laptop computers using standardized software. Information on vital status and location was sought through various tracing sources. In total, 10,778 (79.9 percent) of the implant patients and 3,214 (81.7 percent) of the comparison patients were traced, with 364 being identified as deceased (245 implant patients and 119 comparison subjects). Death certificates were obtained for 91.4 percent and 95.8 percent of the deceased implant and comparison patients, respectively.

Beginning in June 1995, subjects were sent mailed questionnaires requesting information on demographic factors, subsequent plastic surgeries, current health status, and lifestyle factors that could affect health. Respondents were asked whether they had ever received a physician's diagnosis of rheumatoid arthritis, arthritis of another type, scleroderma, systemic lupus erythematosus, Sjögren's syndrome, Raynaud's phenomenon, fibrositis/fibromyalgia, vasculitis, chronic fatigue syndrome, or multiple sclerosis. They were also asked whether they had received any other CTD diagnosis and, if so, which one. For each condition, patients were asked to provide their age at first diagnosis and the physician's name and address. Nonrespondents were given the opportunity to complete questionnaires by telephone. Questionnaires were obtained from 7,447 (70.7 percent) of the living implant patients and 2,203 (71.2 percent) of the comparison patients.

Statistical methods

Person-years were accrued beginning 1 year after initial plastic surgery and continuing through the earliest date of development of a CTD, the date on which the patient was last known to be alive and free of any CTD, or December 31, 1996. Patients with a CTD diagnosed prior to their initial plastic surgery were excluded from analysis of that disease; further evaluation that excluded such patients from all analyses showed no substantial changes in risk estimates. Poisson regression methods (37), as implemented in the Epicure AMFIT module (38), were used to calculate relative risks (implant patients vs. comparison patients), compute 95 percent confidence intervals, and adjust for potentially confounding variables. For all analyses, relative risks were adjusted for age at follow-up, calendar period of follow-up, and race. Other factors, such as age at surgery, year of surgery, time since surgery, or specific predictors of CTDs (education, family history), were included in the regression models, as necessary, for evaluation of their roles as potentially confounding factors or for examination of variations in the relative risk. The final analytical data set, which excluded subjects who developed CTDs within 1 year of initial plastic surgery (59 implant patients and 21 comparison patients) and persons of races other than White or Black (154 implant patients and 44 comparison patients), consisted of 7,234 implant patients and 2,138 comparison patients.

The mortality of the subjects through the end of 1997 was also examined (36).

Medical review of reported CTDs

We attempted to retrieve and review medical records for the CTDs that have been most consistently related to breast implants and for which patient reports indicated persistent elevations in risk over time. Notations regarding implants were blacked out, and extraneous information in the records of comparison patients was similarly marked, to blind the reviewing rheumatologists as to patient implant status. Using a standardized abstract form, two board-certified rheumatologists (L. M. B. and O. D.) reviewed the records to determine their adequacy and to assess whether the patient's history, the physical examination, and radiographic and laboratory findings supported the diagnoses reported. The reviewers assessed the likelihood of each reported diagnosis (likely, unlikely, unable to assess). Instances of disagreement between reviewers were resolved by having both rheumatologists re-review the record and come to consensus. For diagnoses deemed "likely," the reviewers determined whether standardized criteria for rheumatoid arthritis (39) or Sjögren's syndrome (40) were met. For diagnoses deemed "unlikely," the reviewers were asked to indicate a probable alternative diagnosis (chronic fatigue syndrome, fibromyalgia, osteoarthritis, other condition, no condition, or unknown).

RESULTS

Although implant patients were somewhat younger than comparison patients at the time of their plastic surgery (mean

TABLE 1. Relative risk of self-reported connective tissue disorders and other conditions among patients with breast implants in comparison with other plastic surgery patients, southeastern United States, 1960–1996

Condition*	No. of implant patients (n = 7,234) (87,199 person-years)	No. of comparison patients (n = 2,138) (23,724 person-years)	Relative risk†	95% confidence interval
Connective tissue disorders	351	62	2.0	1.5, 2.8
Rheumatoid arthritis	258	49	1.9	1.4, 2.7
Scleroderma	23	3	3.0	0.8, 10.9
Systemic lupus erythematosus	72	10	2.1	1.1, 4.2
Sjögren's syndrome	43	2	11.7	2.5, 54.9
Other conditions				
Other arthritis	724	201	1.3	1.1, 1.6
Raynaud's phenomenon	97	10	2.6	1.3, 5.1
Fibromyalgia	311	57	1.3	0.9, 1.7
Vasculitis	21	4	1.4	0.5, 4.6
Chronic fatigue syndrome	246	27	2.4	1.6, 3.6
Multiple sclerosis	26	5	0.7	0.2, 1.9
Other disorders	202	24	2.5	1.6, 3.9

* Conditions are not mutually exclusive.

† Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960–1964, …, 1990–1994, 1995–1996), and race (White or Black).

ages of 34.6 years and 41.5 years, respectively), the mean years of initial surgery were similar (1983.0 vs. 1984.3). The average length of follow-up was 12.1 years among the implant patients and 11.1 years among the comparison patients. The maximum lengths of follow-up were 31.6 years and 27.6 years among the implant and comparison patients, respectively.

Self-reported conditions

Three hundred fifty-one (4.8 percent) of the implant patients and 62 (2.9 percent) of the comparison patients reported a diagnosis of one of four major CTDs (rheumatoid arthritis, scleroderma, systemic lupus erythematosus, or Sjögren's syndrome), generating a relative risk of 2.0 (95 percent confidence interval (CI): 1.5, 2.8) (table 1). Significant risk elevations were noted for rheumatoid arthritis (relative risk (RR) = 1.9, 95 percent CI: 1.4, 2.7), systemic lupus erythematosus (RR = 2.1, 95 percent CI: 1.1, 4.2), and Sjögren's syndrome (RR = 11.7, 95 percent CI: 2.5, 54.9). Scleroderma was associated with a threefold risk on the basis of 23 implant patients and three comparison subjects. Significant risks were also observed for Raynaud's phenomenon (RR = 2.6, 95 percent CI: 1.3, 5.1) and chronic fatigue syndrome (RR = 2.4, 95 percent CI: 1.6, 3.6). Nonrheumatoid types of arthritis were more commonly reported by the implant patients than by the comparison patients, generating a modestly increased but significant risk (RR = 1.3, 95 percent CI: 1.1, 1.6). Although it was commonly reported, fibromyalgia was not associated with any significant risk (RR = 1.3), nor was the less frequently reported vasculitis (RR = 1.4). A large number of patients reported having "other CTDs," but most were vaguely defined or should not have been considered CTDs (e.g., bursitis, carpal tunnel syndrome). A number of implant patients reported having atypical or undifferentiated (12 implant patients) or mixed (24 implant patients, one comparison patient) CTDs—diagnoses developed for implant patients whose symptoms did not fit recognized diagnostic categories. Specific references to other types of definite CTDs (e.g., polymyalgia rheumatica) were rare and not unusually represented among the implant patients.

We analyzed disease associations according to whether the diseases were reportedly diagnosed prior to or during/after 1992, when the Food and Drug Administration changed the status of breast implants to investigational. The overall risk of the major CTDs was higher for conditions diagnosed during or after 1992 (RR = 2.6) as compared with before 1992 (RR = 1.7), although both risks were significant (table 2). The risks were similar in the two time periods for rheumatoid arthritis, scleroderma, and Sjögren's syndrome, but for a number of conditions the risks were substantially higher for diagnoses occurring in the later period. This was true for lupus, Raynaud's phenomenon, fibromyalgia, chronic fatigue syndrome, and "other CTDs." However, the risk of chronic fatigue syndrome was significantly elevated in both the earlier and the later time periods. Only for one condition, vasculitis, was the relative risk higher (though nonsignificant) for diagnoses in the earlier time period (RR = 2.6), on the basis of 10 reported cases among the implant patients.

In additional analyses, we examined risks for conditions with sufficient numbers of exposed persons by age at, calendar period of, and years since initial implantation (table

TABLE 2. Relative risk* of self-reported connective tissue disorders and other conditions among patients with breast implants in comparison with other plastic surgery patients, by period of diagnosis, southeastern United States, 1960–1996

Condition	Period of diagnosis					
	Before 1992			During or after 1992		
	No. of cases observed†	RR‡	95% CI‡	No. of cases observed†	RR	95% CI
Connective tissue disorders	185	1.7	1.2, 2.5	166	2.6	1.6, 4.1
Rheumatoid arthritis	145	1.9	1.2, 3.0	113	2.0	1.2, 3.3
Scleroderma	13	2.6	0.5, 13.6	10	2.3	0.3, 18.2
Systemic lupus erythematosus	29	0.9	0.4, 2.1	43	5.9	1.4, 24.6
Sjögren's syndrome	12	12.1	1.1, 134	31	10.1	1.4, 75.2
Other conditions						
Other arthritis	397	1.3	1.0, 1.6	327	1.3	1.0, 1.6
Raynaud's phenomenon	47	1.8	0.7, 4.8	50	3.1	1.2, 8.1
Fibromyalgia	156	0.9	0.6, 1.4	155	1.9	1.2, 3.0
Vasculitis	10	2.6	0.3, 22.0	11	1.3	0.4, 5.1
Chronic fatigue syndrome	123	1.9	1.1, 3.2	123	3.3	1.7, 6.3
Multiple sclerosis	10	0.6	0.2, 2.2	6	0.6	0.1, 3.1
Other disorders	82	1.4	0.8, 2.6	120	3.6	1.9, 7.0

* Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960–1964, …, 1990–1994, 1995–1996), and race (White or Black).
† Number of breast implant patients with the disorder.
‡ RR, relative risk; CI, confidence interval.

3). For the major CTDs, there was no evidence of a trend in risk according to any of these parameters. This was also generally true when individual conditions were considered, although for several conditions (e.g., scleroderma, Sjögren's syndrome) the risks were difficult to interpret because of small numbers. We also examined the effects of timing of

TABLE 3. Relative risk* of self-reported connective tissue disorders and other conditions among patients with breast implants in comparison with other plastic surgery patients, according to various time parameters of initial implantation, southeastern United States, 1960–1996

Condition	Age (years) at initial implantation				Calendar year of initial implantation				No. of years since initial implantation			
	<30	30–34	35–39	≥40	<1975	1975–1979	1980–1984	≥1985	<5	5–9	10–14	≥15
Connective tissue disorders	2.3 (94)†	2.0 (89)	3.9‡ (83)	1.8‡ (85)	1.3 (40)	2.2‡ (119)	2.1‡ (125)	2.1‡ (67)	1.6 (61)	1.9‡ (125)	3.9‡ (101)	1.5 (64)
Rheumatoid arthritis	1.9 (68)	4.0 (63)	4.2‡ (68)	1.5‡ (59)	0.8 (27)	2.1‡ (100)	2.2‡ (86)	2.2‡ (45)	1.8 (43)	1.9‡ (91)	3.1‡ (74)	1.1 (50)
Scleroderma	∞ (3)	0.9 (7)	∞ (6)	3.3 (7)	∞ (2)	2.5 (4)	1.5 (11)	∞ (6)	∞ (4)	2.0 (13)	∞ (3)	∞ (3)
Systemic lupus	4.3 (28)	0.9 (20)	1.2 (6)	2.8‡ (18)	∞ (8)	3.9 (17)	2.8 (31)	1.2 (16)	1.2 (15)	1.6 (23)	∞ (25)	∞ (9)
Sjögren's syndrome	∞ (9)	∞ (8)	∞ (12)	8.3‡ (14)	5.7 (5)	∞ (12)	∞ (16)	4.4 (10)	∞ (5)	5.5 (14)	8.3 (14)	∞ (10)
Other conditions												
Other arthritis	1.8 (162)	1.4 (176)	1.5 (181)	1.2 (205)	2.3‡ (90)	1.4‡ (250)	1.2 (258)	1.2 (126)	1.6‡ (149)	1.0 (217)	1.4 (219)	1.8‡ (139)
Raynaud's phenomenon	3.4 (37)	1.3 (20)	4.2 (24)	2.6 (16)	∞ (5)	2.5 (31)	1.5 (39)	10.8‡ (22)	∞ (27)	1.5 (32)	8.4‡ (28)	1.8 (10)
Fibromyalgia	1.3 (103)	1.0 (96)	1.3 (69)	1.4 (43)	3.4 (34)	1.3 (92)	1.0 (109)	1.7 (76)	1.0 (72)	1.3 (113)	1.2 (83)	3.5 (43)
Chronic fatigue syndrome	1.6 (97)	1.3 (59)	3.1 (47)	4.1‡ (43)	∞ (25)	1.5 (75)	1.7 (90)	4.4‡ (56)	2.4 (46)	1.9‡ (83)	1.7 (72)	∞ (45)

* Adjusted for age at follow-up (5-year intervals through age 85 years), calendar period of follow-up (1960–1964, …, 1990–1994, 1995–1996), and race (White or Black).
† Numbers in parentheses, number of breast implant patients with the disorder.
‡ 95% confidence interval excluded 1.0.

TABLE 4. Results of two board-certified rheumatologists' reviews of selected self-reports of rheumatoid arthritis, scleroderma, and Sjögren's syndrome among patients with breast implants and other plastic surgery patients, southeastern United States, 1960–1996

Condition and rheumatologists' assessment of diagnosis	All patients		Patients with breast implants		Comparison patients	
	No.	%	No.	%	No.	%
Rheumatoid arthritis	(*n* = 114)*		(*n* = 97)		(*n* = 17)	
Likely	20	17.5	16	16.5	4	23.5
Unlikely	80	70.2	69	71.1	11	64.7
Unassessable	13	11.4	12	12.4	1	5.9
No consensus	1	0.9	0	0.0	1	5.9
Scleroderma	(*n* = 8)		(*n* = 7)		(*n* = 1)	
Likely	2	25.0	2	28.6	0	0.0
Unlikely	2	25.0	2	28.6	0	0.0
Unassessable	4	50.0	3	42.9	1	100.0
Sjögren's syndrome	(*n* = 20)		(*n* = 19)		(*n* = 1)	
Likely	6	30.0	6	31.6	0	0.0
Unlikely	7	35.0	7	36.8	0	0.0
Unassessable	7	35.0	6	31.6	1	100.0

* Number of medical records that were reviewed by the rheumatologists. In standard chi-squared testing, none of the tests for differences produced significant results.

implantation according to whether conditions were diagnosed prior to or during/after 1992. Given the evidence that breast implants deteriorate over time, we focused on relations by the number of years since initial implantation. This analysis showed no relation with years since implantation for diseases diagnosed prior to 1992 but increasing risks after this time (e.g., for the major CTDs, in comparison with women with less than 5 years of follow-up, the risks were 1.5, 1.6, and 2.0 for 5–9, 10–14, and ≥15 years of follow-up, respectively; comparable risks for women diagnosed before 1992 were 1.2, 1.3, and 0.8). This post-1992 pattern largely reflected trends for rheumatoid arthritis.

Given that rates of location and response varied depending on the source of patients, we subdivided medical practices from which patients were recruited according to their average rates of location (<75 percent, 75–84 percent, and ≥85 percent) and questionnaire completion (<70 percent, 70–74 percent, and ≥75 percent). There appeared to be no consistent pattern of risk according to these groupings. We further grouped practices according to the combination of location rate and response rate. The relative risk for the major CTDs was 2.4 for practices with the highest rates and 1.9 for practices with the lowest rates. We also examined risks for the demographic subgroup with the highest questionnaire response rate (>70 percent)—namely, older White subjects who had undergone surgery after 1981. The risk of major CTDs, as well as the risk of most individual diseases, was similar to overall risks (for the major CTDs, RR = 1.8, 95 percent CI: 1.0, 3.1).

Of the patients who received breast implants, 49.7 percent received silicone gel implants, 34.1 percent received double lumen implants, 12.2 percent received saline implants, and 3.9 percent received other/unspecified types of implants. The relative risk of major CTDs was 2.4 for silicone gel implants (210 events among implant patients; 95 percent CI: 1.8, 3.4), 1.8 for double lumen implants (100 events; 95 percent CI: 1.3, 2.6), 1.7 for saline implants (34 events; 95 percent CI: 1.0, 2.7), and 0.9 for other/unspecified implants (seven events; 95 percent CI: 0.4, 2.1). Risks of individual diseases were also generally somewhat higher for women with silicone gel implants, although the differences by implant type were not significant.

Examination of causes of death showed that none of the implant or comparison patients had a CTD as an underlying or contributory cause of death.

Rheumatologic review of conditions

We attempted to confirm diagnoses of rheumatoid arthritis, scleroderma, and Sjögren's syndrome in physicians' records. Permission for record retrieval was obtained from 70.4 percent of implant patients and 53.7 percent of comparison patients. We retrieved 56.4 percent and 65.5 percent of these patients' records, respectively; the records comprised 114 patients with rheumatoid arthritis, eight with scleroderma, and 20 with Sjögren's syndrome.

Most diagnoses were insufficiently supported, either because the records were incomplete or because clinical criteria were not met (table 4). Consensus review found the diagnosis of rheumatoid arthritis to be "unlikely" for 71.1 percent of implant patients and 64.7 percent of comparison patients. The diagnosis was supported for 16.5 percent of

TABLE 5. Projections of the likely number of cases of connective tissue disorders in the patient population based on the number of reported cases assessed by rheumatologists to represent "likely" diagnoses, southeastern United States, 1960–1996

Condition	Reported no. of cases	% for which medical record was obtained	% for which diagnosis was assessed as "likely"	No. of likely cases identified*	Projected likely no. of cases†
Rheumatoid arthritis, scleroderma, or Sjögren's syndrome					
Implant patients	310	39.7	19.5	24	60
Comparison patients	54	35.2	21.0	4	11
Relative risk	2.2			2.5	2.0
95% confidence interval	1.6, 3.0			0.8, 7.8	0.7, 5.4
Rheumatoid arthritis only					
Implant patients	258	37.6	16.5	16	43
Comparison patients	49	34.7	23.5	4	11
Relative risk	1.9			1.9	1.3
95% confidence interval	1.4, 2.7			0.6, 6.2	0.5, 3.8

* Derived by multiplying the reported number of cases by the percentage of records obtained and the percentage of obtained records with diagnoses assessed as likely.

† Derived by multiplying the reported number of cases by the percentage of obtained records with diagnoses assessed as likely.

implant patients and 23.5 percent of comparison patients. American College of Rheumatology criteria (39) were met by eight of the 16 implant patients and three of the four comparison patients with "likely" diagnoses.

Given the rarity of scleroderma and Sjögren's syndrome, reports were difficult to assess, particularly among comparison subjects. Furthermore, a number of reports of both diseases were classified as unassessable. For Sjögren's syndrome, this was often due to the absence of diagnostic tests, including biopsies and serologic testing needed to distinguish Sjögren's syndrome from other causes of xerostomia and dry eyes.

For those records with diagnoses assessed as unlikely, each reviewer was asked to assign a probable alternative diagnosis. For reports of rheumatoid arthritis, osteoarthritis was assigned most often among the implant patients (37.7 percent), followed by fibromyalgia (24.6 percent) and both osteoarthritis and fibromyalgia (14.5 percent). Comparable percentages among the comparison patients were 63.6 percent, 0 percent, and 9.1 percent. Among the seven unlikely reported cases of Sjögren's syndrome among implant patients, two were considered potential cases of fibromyalgia, one was considered osteoarthritis, and one was considered both diseases. Both reported cases of unlikely scleroderma among the implant patients were considered possible cases of fibromyalgia.

Range of risk estimates

We calculated incidence rates and relative risks for diseases that were considered likely by both reviewers (table 5). For rheumatoid arthritis, scleroderma, and Sjögren's syndrome combined, the relative risk was 2.5 (95 percent CI: 0.8, 7.8) on the basis of 24 implant patients and four comparison patients. Rheumatoid arthritis was the major contributor to this risk, occurring among 16 implant patients and four comparison patients (RR = 1.9, 95 percent CI: 0.6, 6.2). For comparative purposes, the relative risks based on self-reports were 2.2 (95 percent CI: 1.6, 3.0) for all three conditions and 1.9 (95 percent CI: 1.4, 2.7) for rheumatoid arthritis. The absence of confirmed cases of either scleroderma or Sjögren's syndrome among the comparison patients precluded derivation of reliable point estimates, but the lower 95 percent confidence limits for both of these risks were 0.4.

Given concerns that we were unable to retrieve all of the medical records for self-reported conditions, we also derived estimates of risk for all patients using confirmation rates based on patients with retrieved records. This analysis gave us an estimated relative risk of 2.0 (95 percent CI: 0.7, 5.4) for all three conditions and 1.3 (95 percent CI: 0.5, 3.8) for rheumatoid arthritis.

DISCUSSION

The design of this investigation and the characteristics of the assembled cohort offered many advantages for studying cancer risk and cause-specific mortality in relation to cosmetic breast implant surgery, the primary objectives of the study. These features include large numbers of implant patients (representing all patients from specific practices), extended follow-up, a practice-based comparison group, and the availability of questionnaire information on covariates. These features provide advantages in assessing the relation

of breast implants to CTDs as well. However, in contrast to the relation between cancer and mortality, there are no well-accepted age-, race-, sex-, and calendar-time-specific population incidence rates for CTDs. Thus, our study was dependent on comparisons of rates in the implant and comparison patients; for rare diagnoses (the majority), this involved small numbers and unreliable rates. In addition, the complex clinical presentation of many CTDs and the variable criteria used to diagnose these diseases make reliable identification of cases difficult.

In interpreting the results of this study, potential effects of selection, recall, and surveillance biases must be considered. Of particular concern is the fact that many of the disease relations were primarily associations with conditions reportedly diagnosed in 1992 or later. The difference in risks between the two time periods was most apparent for lupus, Raynaud's phenomenon, fibromyalgia, and chronic fatigue syndrome, the most graphic example being lupus: The relative risk was 0.9 in the era prior to extensive publicity and 5.9 afterward. Although trends by time of diagnosis could reflect the influence of implant leakage, given the evidence of deterioration of implants over time (41), specific analyses that addressed relations by latency showed increasing risks' being restricted to post-1992 diagnoses. This suggests that the publicity surrounding possible disease associations in the early 1990s may have contributed to the observed time trends.

Three conditions—rheumatoid arthritis, scleroderma, and Sjögren's syndrome—continued to show elevations in risk even in the earlier time period and were of concern given speculations from other investigations of a link with breast implants. However, self-reports of CTDs for all patients, with or without implants, are subject to reporting and diagnostic biases and must be cautiously interpreted. Our confirmed risks were dependent on obtaining consent to retrieve records and on retrieving the relevant records when consent was received—challenges also experienced in another investigation (42). In analysis based on confirmed records, which involved considerably smaller sample sizes and may have been influenced by a variety of selection factors, the risk for the three conditions was 2.5; it dropped to 2.0 when we also factored in completeness of record retrieval. Both estimates were nonsignificant. Recognized differences in lifestyle factors between implant and comparison patients (43) further complicated the interpretation of these risks, especially given the absence of many identified risk factors for these CTDs. Thus, the influence that confounding factors might have had on the risk estimates cannot be dismissed.

We had the most power to evaluate risks for rheumatoid arthritis. On the basis of self-reports, we saw no trends in risk with any time-related parameters, including interval since implantation. This raises questions regarding biologic plausibility. Several investigations have suggested small but nonsignificant risk increases for this disease among implant patients (17, 23, 27, 35), though several other cohort (28–30) and case-control (21, 44) studies have not supported a connection. However, many of these investigations had small sample sizes and short follow-up times. In one of the investigations that suggested a small increase in risk (23), subsequent confirmation of reported CTDs found evidence of overreporting; only 22.7 percent of the self-reported cases were confirmed (42). This was similar to our investigation, wherein retrieval of medical records confirmed only 17 percent of the reported cases, possibly reflecting a lack of awareness by the public of differences between rheumatoid arthritis and other types of arthritis (e.g., osteoarthritis). Further complicating the interpretation of self-reports of rheumatoid arthritis in our study was the fact that a somewhat higher percentage of cases were confirmed in the comparison patients than in the implant patients. When analyses were restricted to cases judged likely by the two rheumatologists, the risk fell to less than 2 and became nonsignificant. Furthermore, when we factored in our ability to retrieve records to confirm self-reports, our estimate of risk was 1.3, also not significant.

On the basis of clinical studies, the CTD that has been most consistently related to breast implants is scleroderma. This condition is difficult to study epidemiologically given its rarity in the general population, with estimates of annual disease incidence in females of 1.6 cases per 100,000 (45). In the largest cohort study, a relative risk of 1.84 (95 percent CI: 0.98, 3.5) was found on the basis of 10 observed cases among implant patients (23). The relation of this condition to breast implants has frequently been assessed in case-control investigations, with most not showing a relation (16, 21, 24, 46). In our study, 23 implant patients and three comparison patients reported scleroderma, resulting in a nonsignificant threefold risk elevation. Of the retrieved medical records, only 29 percent of cases among the implant patients were assessed as likely, for a total of two confirmed cases. The one comparison patient record failed to support the diagnosis. Thus, with no reliable estimate of comparison rates, we cannot address the likelihood of an association. What is clear is that any excess risk of scleroderma in implant recipients, if present, is likely to be small in absolute terms.

Sjögren's syndrome was also of concern on the basis of prior clinical and epidemiologic literature, as well as preliminary self-report findings in this study. This is also a rare condition, with an annual estimated incidence of four cases per 100,000 population (47). One meta-analysis (48) noted a significant increase in this condition, largely reflecting risks from one investigation (23). Our relative risk for Sjögren's syndrome based on self-reports was the largest of any observed, but whether any excess risk would remain for validated diagnoses is unclear. As with scleroderma, any increase in absolute risk, should it remain, would be small.

In this investigation, we also assessed the risks of fibromyalgia and vasculitis, because implant patients have reported symptoms often associated with these diseases (49–51). Furthermore, one study found a relation between implant leakage and increased risk of fibromyalgia (41). Self-reports of fibromyalgia or vasculitis were not found to be related to any sizeable risk in our study. However, chronic fatigue syndrome was associated with a modest increase in risk. This relation, though substantially more pronounced for diagnoses reported during or after 1992, was also present for earlier diagnoses. The diagnostic complexities of chronic fatigue syndrome are well recognized (52); the symptoms leading to medical assistance and the criteria used to confirm

the disease are associated with considerable uncertainty. Since this was not a condition that we attempted to confirm, we were unable to assess the extent to which defining criteria were present.

Our study was designed to assess only established CTDs. However, clinical observations (49–51, 53–55) have suggested that breast implants may lead to a new condition that does not meet established criteria for a recognized CTD. Although results from a case-control investigation provided some support for this (56), several recent record-linkage studies in Scandinavia failed to note unusual symptoms among women with breast implants (57, 58). Study of the issue is complex, especially since the suggestion of this entity is usually prompted by the presence of a breast implant. Appropriate evaluation would require a study design that included standardized histories and examinations in a large sample of implant patients and appropriate comparison patients.

This investigation confirmed the complexities of evaluating the relation between breast implants and the risk of CTDs. It is clear that a variety of selection and reporting biases may be involved, as evidenced in the present study by overreporting of conditions by both implant and comparison patients and the difficulty of confirming conditions according to defined clinical criteria. Our investigation had the most power to address relations with rheumatoid arthritis. Therefore, it is of interest that our risk estimates (on the basis of cases considered likely by expert chart review) were between 1.3 and 1.9 and not statistically significant. Confidence intervals in previous studies addressing the relation of breast implants to rheumatoid arthritis have included this level of risk. Thus, future studies designed to resolve the question of a possible association between implants and rheumatoid arthritis or other CTDs would need to be very large (especially to address such rare outcomes as scleroderma and Sjögren's syndrome) and include well-validated and documented cases and unbiased assessments of exposure. To this end, the levels of risk that we observed for CTDs may be useful in determining sample sizes needed.

REFERENCES

1. Brinton LA, Lubin JH, Burich MC, et al. Breast cancer following augmentation mammoplasty (United States). Cancer Causes Control 2000;11:819–27.
2. Brinton LA, Lubin JH, Burich MC, et al. Cancer risk at sites other than the breast following augmentation mammoplasty. Ann Epidemiol 2001;11:248–56.
3. McLaughlin JK, Nyren O, Blot WJ, et al. Cancer risk among women with cosmetic breast implants: a population-based cohort study in Sweden. J Natl Cancer Inst 1998;90:156–8.
4. Mellemkjaer L, Kjoller K, Friis S, et al. Cancer occurrence after cosmetic breast implantation in Denmark. Int J Cancer 2000; 88:301–6.
5. Baldwin CM Jr, Kaplan EN. Silicone-induced human adjuvant disease? Ann Plast Surg 1983;10:270–3.
6. Copeland M, Kressel A, Spiera H, et al. Systemic inflammatory disorder related to fibrous breast capsules after silicone implant removal. Plast Reconstr Surg 1993;92:1179–81.
7. Fock KM, Feng PH, Tey BH. Autoimmune disease developing after augmentation mammoplasty: report of 3 cases. J Rheumatol 1984;11:98–100.
8. Marik PE, Kark AL, Zambakides A. Scleroderma after silicone augmentation mammoplasty: a report of 2 cases. S Afr Med J 1990;77:212–13.
9. Okano Y, Nishikai M, Sato A. Scleroderma, primary biliary cirrhosis, and Sjögren's syndrome after cosmetic breast augmentation with silicone injection: a case report of possible human adjuvant disease. Ann Rheum Dis 1984;43:520–2.
10. Sahn EE, Garen PD, Silver RM, et al. Scleroderma following augmentation mammoplasty: report of a case and review of the literature. Arch Dermatol 1990;126:1198–202.
11. Sergott TJ, Limoli JP, Baldwin CM Jr, et al. Human adjuvant disease, possible autoimmune disease after silicone implantation: a review of the literature, case studies, and speculation for the future. Plast Reconstr Surg 1986;78:104–14.
12. Spiera H, Kerr LD. Scleroderma following silicone implantation: a cumulative experience of 11 cases. J Rheumatol 1993; 20:958–61.
13. van Nunen SA, Gatenby PA, Basten A. Post-mammoplasty connective tissue disease. Arthritis Rheum 1982;25:694–7.
14. Varga J, Schumacher HR, Jimenez SA. Systemic sclerosis after augmentation mammoplasty with silicone implants. Ann Intern Med 1989;111:377–83.
15. Weiner SR, Paulus HE. Chronic arthropathy occurring after augmentation mammoplasty. Plast Reconstr Surg 1986;77: 185–92.
16. Burns CJ, Laing TJ, Gillespie BW, et al. The epidemiology of scleroderma among women: assessment of risk from exposure to silicone and silica. J Rheumatol 1996;23:1904–11.
17. Edworthy SM, Martin L, Barr SG, et al. A clinical study of the relationship between silicone breast implants and connective tissue disease. J Rheumatol 1998;25:254–60.
18. Englert H, Joyner E, McGill N, et al. Women's health after plastic surgery. Intern Med J 2001;31:77–89.
19. Gabriel SE, O'Fallon WM, Kurland LT, et al. Risk of connective-tissue diseases and other disorders after breast implantation. N Engl J Med 1994;330:1697–702.
20. Giltay EJ, Bernelot Moens HJ, Riley AH, et al. Silicone breast prostheses and rheumatic symptoms: a retrospective follow up study. Ann Rheum Dis 1994;53:194–6.
21. Goldman JA, Greenblatt J, Joines R, et al. Breast implants, rheumatoid arthritis, and connective tissue diseases in a clinical practice. J Clin Epidemiol 1995;48:571–82.
22. Greenland S, Finkle WD. A retrospective cohort study of implanted medical devices and selected chronic diseases in Medicare claims data. Ann Epidemiol 2000;10:205–13.
23. Hennekens CH, Lee IM, Cook NR, et al. Self-reported breast implants and connective-tissue diseases in female health professionals: a retrospective cohort study. JAMA 1996;275:616–21.
24. Hochberg MC, Perlmutter DL, Medsger TA Jr, et al. Lack of association between augmentation mammoplasty and systemic sclerosis (scleroderma). Arthritis Rheum 1996;39:1125–31.
25. Kjoller K, Friis S, Mellemkjaer L, et al. Connective tissue disease and other rheumatic conditions following cosmetic breast implantation in Denmark. Arch Intern Med 2001;161:973–9.
26. Lai S, Goldman JA, Child AH, et al. Fibromyalgia, hypermobility, and breast implants. J Rheumatol 2000;27:2237–41.
27. Nyren O, Yin L, Josefsson S, et al. Risk of connective tissue disease and related disorders among women with breast implants: a nation-wide retrospective cohort study in Sweden. BMJ 1998;316:417–22.
28. Park AJ, Black RJ, Sarhadi NS, et al. Silicone gel-filled breast implants and connective tissue diseases. Plast Reconstr Surg 1998;101:261–8.

29. Sanchez-Guerrero J, Colditz GA, Karlson EW, et al. Silicone breast implants and the risk of connective-tissue diseases and symptoms. N Engl J Med 1995;332:1666–70.
30. Schusterman MA, Kroll SS, Reece GP, et al. Incidence of autoimmune disease in patients after breast reconstruction with silicone gel implants versus autogenous tissue: a preliminary report. Ann Plast Surg 1993;31:1–6.
31. Strom BL, Reidenberg MM, Freundlich B, et al. Breast silicone implants and risk of systemic lupus erythematosus. J Clin Epidemiol 1994;47:1211–14.
32. Weisman MH, Vecchione TR, Albert D, et al. Connective-tissue disease following breast augmentation: a preliminary test of the human adjuvant disease hypothesis. Plast Reconstr Surg 1988;82:626–30.
33. Wells KE, Cruse CW, Baker JL Jr, et al. The health status of women following cosmetic surgery. Plast Reconstr Surg 1994; 93:907–12.
34. Williams HJ, Weisman MH, Berry CC. Breast implants in patients with differentiated and undifferentiated connective tissue disease. Arthritis Rheum 1997;40:437–40.
35. Wolfe F, Anderson J. Silicone filled breast implants and the risk of fibromyalgia and rheumatoid arthritis. J Rheumatol 1999;26: 2025–8.
36. Brinton LA, Lubin JH, Burich MC, et al. Mortality among augmentation mammoplasty patients. Epidemiology 2001;12: 321–6.
37. Breslow NE, Day NE, eds. Statistical methods in cancer research. Vol 2. The design and analysis of cohort studies. (IARC Scientific Publication no. 82). Lyon, France: International Agency for Research on Cancer, 1987.
38. Preston DL, Lubin JH, Pierce DA, et al. EPICURE: risk regression and data analysis software. Seattle, WA: HiroSoft International Corporation, 1996.
39. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
40. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.
41. Brown SL, Pennello G, Berg WA, et al. Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women. J Rheumatol 2001;28:996–1003.
42. Karlson EW, Lee IM, Cook NR, et al. Comparison of self-reported diagnosis of connective tissue disease with medical records in female health professionals: The Women's Health Cohort Study. Am J Epidemiol 1999;150:652–60.
43. Brinton LA, Brown SL, Colton T, et al. Characteristics of a population of women with breast implants compared with women seeking other types of plastic surgery. Plast Reconstr Surg 2000;105:919–27.
44. Dugowson CE, Daling J, Koepsell TD, et al. Silicone breast implants and risk for rheumatoid arthritis. (Abstract). Arthritis Rheum 1992;35(suppl):S66.
45. Michet CJ Jr, McKenna CH, Elveback LR, et al. Epidemiology of systemic lupus erythematosus and other connective tissue diseases in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc 1985;60:105–13.
46. Englert H, Morris D, March L. Scleroderma and silicone gel breast prostheses—the Sydney study revisited. Aust N Z J Med 1996;26:349–55.
47. Pillemer SR, Matteson EL, Jacobsson LT, et al. Incidence of physician-diagnosed primary Sjögren syndrome in residents of Olmsted County, Minnesota. Mayo Clin Proc 2001;76:593–9.
48. Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med 2000;342:781–90.
49. Borenstein D. Siliconosis: a spectrum of illness. Semin Arthritis Rheum 1994;24(suppl 1):1–7.
50. Solomon G. A clinical and laboratory profile of symptomatic women with silicone breast implants. Semin Arthritis Rheum 1994;24(suppl 1):29–37.
51. Vasey FB, Havice DL, Bocanegra TS, et al. Clinical findings in symptomatic women with silicone breast implants. Semin Arthritis Rheum 1994;24(suppl 1):22–8.
52. De Becker P, McGregor N, De Meirleir K. A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome. J Intern Med 2001;250:234–40.
53. Cuellar ML, Gluck O, Molina JF, et al. Silicone breast implant-associated musculoskeletal manifestations. Clin Rheumatol 1995;14:667–72.
54. Lu LB, Shoaib BO, Patten BM. Atypical chest pain syndrome in patients with breast implants. South Med J 1994;87:978–84.
55. Shoaib BO, Patten BM, Calkins DS. Adjuvant breast disease: an evaluation of 100 symptomatic women with breast implants or silicone fluid injections. Keio J Med 1994;43:79–87.
56. Laing TJ, Schottenfeld D, Lacey JV Jr, et al. Potential risk factors for undifferentiated connective tissue disease among women: implanted medical devices. Am J Epidemiol 2001;154: 610–17.
57. Fryzek JP, Signorello LB, Hakelius L, et al. Self-reported symptoms among women after cosmetic breast implant and breast reduction surgery. Plast Reconstr Surg 2001;107:206–13.
58. Jensen B, Bliddal H, Kjoller K, et al. Rheumatic manifestations in Danish women with silicone breast implants. Clin Rheumatol 2001;20:345–52.